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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/681,086	10/08/2003	Hans-Peter Hohmann	20606 US (C038435/0111674	7182

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Stephen M. Haracz
BRYAN CAVE LLP
1290 Avenue of the Americas
New York, NY 10104-3300

EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/681,086	HOHMANN ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-30 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-26 and 32* is/are rejected.

7)☒ Claim(s) *27-30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Request for Continued Examination (RCE) filed on May 24, 2007 under 37 CFR 1.114 is acknowledged. An action on the RCE follows.

Status of the Claims

2. Claims 23-30 and 32 are pending.

Applicants' amendment filed May 24, 2007 is acknowledged. Applicants' response has been fully considered. Claim 23 has been amended, and claim 31 has been cancelled. Therefore, claims 23-30 and 32 are examined.

Withdrawn Claim Rejections - 35 USC § 112

3. The previous rejection of claim 31 under 35 U.S.C. 112, first paragraph, scope enablement and written description, is withdrawn in view of applicant's cancellation of the claims in the amendment filed May 24, 2007.

Maintained Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 23-26 and 32 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for a process for decoupling production of a specific target fermentation product (i.e., riboflavin) from biomass production in a fermentation medium, the method comprising: (a) providing a recombinantly produced microorganism of bacillus that contains a polynucleotide sequence which encodes biosynthetic enzymes for the target fermentation product (i.e., riboflavin), (b) introducing a specific mutated polynucleotide

sequence such as SEQ ID NO:1 causing a biotin auxotrophy into the microorganism to control biomass production, and (c) supplying the medium with unlimited amount of substrates for producing the riboflavin and with a limited amount of biotin complementing the auxotrophy; and a microorganism made by the process, does not reasonably provide enablement for a process for decoupling production of a target fermentation product (i.e., riboflavin) from biomass production in a fermentation medium, the method comprising: (a) providing a recombinantly produced microorganism of bacillus that contains a polynucleotide sequence which encodes biosynthetic enzymes for the target fermentation product (i.e., riboflavin), (b) introducing a mutation causing biotin auxotrophy into the microorganism to control biomass production, and (c) supplying the medium with unlimited amount of substrates for producing the riboflavin and with a limited amount of biotin complementing the auxotrophy; and a microorganism made by the process, where the mutation (or the mutated polynucleotide) causing biotin auxotrophy is not identified. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 23-26 and 32 are directed to a process for decoupling production of a target fermentation product from biomass production in a fermentation medium using a recombinantly produced microorganism of bacillus comprising a polynucleotide sequence which encodes biosynthetic enzymes for the target fermentation product, and introducing a mutation causing a biotin auxotrophy into the microorganism; and a microorganism made by the process, wherein the target fermentation product is riboflavin. The specification, however, only discloses cursory conclusions without data supporting the findings, which state that the present invention provides

a process for decoupling production of a target fermentation product from biomass production in a fermentation medium. This process includes providing a recombinantly produced microorganism that has been engineered to contain a polynucleotide sequence which encodes the biosynthetic enzymes for a target fermentation product, where the maximal production of the target fermentation product is dependent on an unlimited supply of a target fermentation product substrate for the microorganism; and then an auxotrophy is introduced into the microorganism to control biomass production by limiting the concentration of a substrate complementing the auxotrophy in the fermentation medium; and a fermentation production microorganism made by the process. There are no indicia that the present application enables the full scope of the claims in view of the claimed method as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance to enable the full scope of the claims. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the presence or absence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the mutations or the mutated polynucleotides that cause biotin auxotrophy, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

While the specification describes introducing a specific biotin auxotroph mutant construct comprising SEQ ID NO:1 into a riboflavin production microorganism RB50 containing multiple copies of pRF69, culturing fermentations, and measuring biomass and riboflavin production at different biotin concentrations (see Examples 1-3), the specification has not identified various mutated polynucleotides that cause biotin auxotrophy, and there is no structure/activity correlation shown in the mutated polynucleotides.

(3). The state of the prior art and relative skill of those in the art:

The related art (references on pages 1-4 of the specification) teach recombinant production of riboflavin and genes involved in the riboflavin biosynthetic pathways; and the art (e.g., Bower et al. U.S. Patent 6,303,377) shows the genes of the biotin biosynthetic operon of *Bacillus subtitis*. However, the art does not disclose the mutation in the genes of the biotin biosynthesis that cause biotin auxotrophy. Since the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide teachings on identification of mutations in the polynucleotides of biotin biosynthesis that cause biotin auxotrophy.

(4). Predictability or unpredictability of the art:

The claims encompass a process for decoupling production of a target fermentation product (i.e., riboflavin) from biomass production in a fermentation medium using a recombinantly produced microorganism of bacillus comprising a polynucleotide sequence which encodes biosynthetic enzymes for the target fermentation product, and introducing a mutation causing a biotin auxotrophy into the microorganism; and a microorganism made by the process. Since the specification discloses only one mutated polynucleotide of SEQ ID NO:1 that causes

biotin auxotrophy, and there is no structure/activity correlation established for the mutated polynucleotides, thus the sequences of the mutated polynucleotides of biotin biosynthesis that cause biotin auxotrophy are unpredictable.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a process for decoupling production of a target fermentation product (i.e., riboflavin) from biomass production in a fermentation medium using a recombinantly produced microorganism of bacillus comprising a polynucleotide sequence which encodes biosynthetic enzymes for the target fermentation product, and introducing a mutation causing a biotin auxotrophy into the microorganism; and a microorganism made by the process. The specification describes introducing a specific biotin auxotroph mutant construct comprising SEQ ID NO:1 into a riboflavin production microorganism RB50 containing multiple copies of pRF69, culturing fermentations, and measuring biomass and riboflavin production at different biotin concentrations (see Examples 1-3). However, the specification has not identified any other mutated polynucleotides that cause biotin auxotrophy. Moreover, there are no working examples demonstrating the use of various recombinantly produced microorganisms transformed with various mutated polynucleotides that cause biotin auxotrophy. Since the specification does not provide sufficient teachings on various mutated polynucleotides that cause biotin auxotrophy in the recombinantly produced microorganisms of bacillus, and there is no structure/activity correlation established for the mutated polynucleotides, it is necessary to carry out undue experimentation to identify the mutated polynucleotides that cause biotin auxotrophy from numerous polynucelotides having mutations.

(6). Nature of the Invention

The scope of the claim encompasses a process for decoupling production of a target fermentation product from biomass production in a fermentation medium using a recombinantly produced microorganism of a bacillus and introducing a biotin auxotophy into the microorganism, but the specification does not provide sufficient teachings on the identities of the mutated polynucleotides that cause biotin auxotrophy. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working example does not demonstrate the claimed method associated with variants, the teachings in the specification are limited, and the sequences of biotin auxotrophy-causing polynucleotides are unpredictable, and therefore, it is necessary to carry out undue experimentation to identify the functional mutated polynucleotides.

Response to Arguments

Applicant indicates claim 23 has been amended to recite (1) that the recombinantly produced microorganism is a Bacillus, (2) that biotin is the specific auxotrophy, and (3) that riboflavin is the specific target fermentation product. Applicant further asserts that the genes involved in biotin biosynthesis are well known to those skilled in the art, in view of the specification and the general knowledge in the art, undue experimentation would not be required to generate mutants and test them for biotin auxotrophy. For example, the specification discloses that the mutation causing auxotrophic growth may be introduced using any convenient means (See p. 8, lines 16-19), and simple screens for confirming an auxotrophy (See p. 12, lines 18-20). And, specific exemplification of a process for decoupling production of riboflavin from biomass production with biotin auxotrophy is disclosed (See, e.g., pp. 15-18; Examples 1-3; and Figs. 1-

4). Moreover, the level of knowledge and skill in this art is high. Thus, in view of the claim amendments, the clear disclosure in the specification of how to make biotin auxotrophs that produce riboflavin, and the acknowledged high degree of skill and knowledge in the art, the claims, as amended, are sufficiently enabled (pages 6-9 of the response).

Applicant's response has been fully considered, however, the arguments are not persuasive because of the following reasons. While the genes involved in biotin biosynthesis are known in the art, a convenient means may be used to introduce a mutation in the genes involved in biotin biosynthesis, and a screening method may be used to confirm a biotin auxotrophy, but there is no the structure/activity correlation for the mutated polynucleotides involved in biotin biosynthesis, and the number of possible mutations in the biotin biosynthesis genes to be tested is virtually endless. Thus, a skilled person would not know how to choose a proper mutated polynucleotide that cause biotin auxotrophy from unlimited number of mutated polynucleotides. Therefore, it is necessary to have additional guidance regarding the structure/activity correlation for the mutated polynucleotides and to carry out undue experimentation to identify the functional mutated polynucleotides. Thus, the full scope of the claims are not enabled.

5. Claims 23-26 and 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 23-26 and 32 are directed to a process for decoupling production of a target fermentation product from biomass production in a fermentation medium using a recombinantly

produced microorganism of bacillus comprising a polynucleotide sequence which encodes biosynthetic enzymes for the target fermentation product, and introducing a mutation causing a biotin auxotrophy into the microorganism, wherein the target fermentation product is riboflavin; and a microorganism made by the process.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

While the specification indicates that the invention provides a process for decoupling production of a target fermentation product from biomass production in a fermentation medium by introducing a specific biotin auxotroph mutant construct comprising SEQ ID NO:1 into *bacillus subtilis* RB50 containing multiple copies of the engineered *rib* operon pRF69, culturing

fermentations, and measuring biomass and riboflavin production at different biotin concentrations, which shows the product yield (i.e., the amount of riboflavin produced on the consumed glucose) is 33% higher in the decoupled process to the coupled process (see Examples 1-3), the specification does not disclose a genus of variants for mutated polynucleotides that cause biotin auxotrophy in a transformed microorganism. A single species of SEQ ID NO:1 (RB50::[pRF69]Bio$^-$ transformed with SEQ ID NO:1 at different biotin concentration to produce riboflavin; Example 3) does not provide written description for the genus of variants of mutated polynucleotides that cause biotin auxotrophy in the claimed method because numerous mutations can occur in the polynucleotides involved in biotin biosynthesis, and there is no way to predict the sequence of the mutated polynucleotide that would cause biotin auxotrophy due to lack of information in the structure/function correlation. Without guidance on the structure of mutated polynucleotide sequence that causes biotin auxotrophy, and its structure to function/activity correlation, one skilled in the art would not know the identities of the functional polynucleotide variants from numerous mutated polynucleotides. The lack of description on the structures of the mutated polynucleotide sequences that cause biotin auxotrophy, and the lack of representative species as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

Response to Arguments

Applicant indicates claim 23 has been amended to recite (1) that the recombinantly produced microorganism is a Bacillus, (2) that biotin is the specific auxotrophy, and (3) that riboflavin is the specific target fermentation product. Applicant further asserts that the Examiner

has acknowledged that methods for making recombinant riboflavin were known, that the genes involved in the riboflavin biosynthetic pathway were known, and that methods for making auxotrophs were known. Coupled to the already acknowledged high level of knowledge and skill in the art, the present specification discloses how to make mutations that may lead to auxotrophs (See p. 8, lines 16-19), simple assays for confirming an auxotrophy (p. 12, lines 18-20), exemplification of the specific biotin auxotroph (pp. 15-18; Examples 1-3; and Figs. 1-4), and how to identify bacillus strains that would fall within the scope of amended claim 23 (pages 11, 12, 14; Examples 1-3). Furthermore, the specification provides ample information on the structures of biotin auxotrophs and how to identify them (See pages 11-18 and Examples 1-3). In view of the foregoing, the Applicants were in possession of the full scope of the instantly claimed invention at the time the application was filed (pages 9-11 of the response).

Applicant's response has been fully considered, however, the arguments are not persuasive because of the following reasons. While the genes involved in biotin biosynthesis are known in the art, a convenient means may be used to introduce a mutation in the genes involved in biotin biosynthesis, and a screening method may be used to confirm a biotin auxotrophy, the specification does not disclose the structure/activity correlation for the mutated polynucleotides, and the number of possible mutations in the biotin biosynthesis genes to be tested is virtually endless. Furthermore, the specification only discloses one specific sequence of SEQ ID NO:1 as the mutated polynucleotide that causes biotin auxotrophy, while MPEP § 2163 states that when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Since numerous mutations can be introduced into the biotin biosynthesis genes, and there is no structure to function/activity correlation established for

the mutated polynulceotides, a skilled person would not know how to choose a proper mutated polynucleotide that cause biotin auxotrophy from unlimited number of mutated polynucleotides. Without description on the structures of mutated polynucleotides that cause biotin auxotrophy, and the lack of representative species as encompassed by the claims, a skilled artisan would not recognize applicants were in possession of the claimed invention.

New Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 23 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claims 23 and 32 are indefinite because of the use of the term "mutation". The term cited renders the claim indefinite, it is unclear where this mutation occurs. Claim 32 is included in the rejection because it is dependent on a rejected claim and does not correct the deficiency of the claim from which it depends.

Claim Objections

8. Claims 27-30 are objected to because the claims are dependent from a rejected claim.

Conclusion

9. Claims 23-26 and 32 are rejected; and claims 27-30 are objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Bragdon can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Primary Patent Examiner

CHIH-MIN KAM
PRIMARY EXAMINER

CMK
August 3, 2007